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Original Article

The Relation Between D-Dimer, HS-CRP, and ACE Inhibitor to Severity, Reinfection, and Mortality of COVID-19 Patients

Novita Silvana Thomas [1], ***Jatu Aphridasari*** [1], ***Ana Rima Setijadi*** [1]

[1] *Departemen Pulmonologi dan Kedokteran Respirasi Fakultas Kedokteran Universitas Sebelas Maret, RSUD dr. Moewardi, Surakarta, Indonesia*

Abstract

Background: COVID-19 reinfection has been found although the data is not clear yet. Pandemic conditions caused limited facilities and infrastructure so that biomarkers are an option. Research on biomarkers and the use of ACE inhibitor drugs in COVID-19 patients has not been widely in Indonesia.

Methods: The retrospective cohort study used medical record data of confirmed COVID-19 patients treated at Dr. Moewardi Hospital for the period January to March 2022. Living patients are confirmed for reinfection until November 2022.

Results: The study involved 524 confirmed medical records of COVID-19 patients. After exclusion and inclusion criteria, 517 medical records were obtained. D-Dimer cut off values ≥2435 were significantly related to severity (OR=2.05; 95%CI=1.38-3.06; p=<0.001) and mortality (OR=2.89; 95%CI=1.95-4.27; p=<0.001) of COVID-19 patients. Hs-CRP levels ≥4.59 were significantly associated with mortality of COVID-19 patients. (OR=1.82; 95%CI=1.23-2.69; p=0.003. The use of ACE inhibitors (OR=0.55; 95%CI=0.33-0.89; p=0.015) is a protective factor from mortality, but increases the risk of reinfection (OR=3.11; 95%CI=1.16-8.36); p=0.034).

Conclusion: D-Dimer and Hs-CRP biomarkers can be considered as predictor biomarkers of the severity and mortality of COVID-19 patients. Although the use of ACE inhibitors increases the risk of reinfection, it reduces the risk of mortality due to COVID-19.

Keywords: D-Dimer, HS-CRP, ACE Inhibitor, Reinfection, COVID-19

Corresponding Author:
Novita Silvana Thomas I
Department of Pulmonology and Respiration Medicine, Faculty of Medicine, Sebelas Maret, Moewardi Hospital, Surakarta, Indonesial
silvana.thomas@yahoo.com

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Severe acute respiratory syndrome coronavirus-2 causes deaths and increasing confirmed cases despite global prevention efforts.[1] World Health Organization (WHO) global data shows more than 504,4 million confirmed cases on April 20, 2022 and 6,2 million confirmed cases died.[2] Data in Indonesia according to the Satuan Tugas Penanganan COVID-19 as of June 23, 2021 shows more than 6,3 million confirmed cases and 157,377 deaths.[3]

COVID-19 reinfection in individuals have been found and are still under study. Azam 2020 showed the incidence of recurrent positive SARS-CoV-2 infection ranged from 7,3 to 21,4 percent (%).[4] Ozaras 2020 found patients experiencing a recurrent positive real-time reverse-transcription polymerase chain reaction (RT-PCR) with a previous history of symptom improvement and negative RT-PCR results.[5] Gao 2021 showed old age and women were at risk of recurrent positive COVID-19.[6] Adrielle et al., 2021 found reinfection giving more severe symptoms than the previous episode. Risk factors that play a role in reinfection are health care worker and having blood type A. Comorbid hypertension, obesity, diabetes, and asthma are not associated with reinfection but affect the clinical severity of COVID-19 reinfection.[7] Qureshi et al., 2022 found reinfection ratio about 0.7% from 9119 patients, the average period of positive test results was 116 ± 21 days. COVID-19 reinfection deaths were 3.2%.[8] Many countries have confirmed reinfections raising questions about the effectiveness of vaccinations.[9]

Mortality ratio from COVID-19 estimated at 3.4% and comorbid conditions increase the risk of death.[10] A meta-analysis study by Bolin et al., 2020

showed five diseases that increase the risk of COVID-19 are hypertension, diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular disease, and cerebrovascular disease.[11] Petrovic 2020 found cardiovascular complications were the most comorbid covid-19 patients of critical degrees at 22.2–31%.[12] Djaharuddin 2020 showed mortality ratio of hospitalized COVID-19 patients about 17.18%. Male and age ≥60 years have higher mortality. Hypertension, cardiovascular disease, and diabetes are comorbidities found in COVID-19 patients who died.[13]

COVID-19 pandemic causes limited facilities and infrastructure so biomarkers are an option to minimize exposure to health workers and if facilities are not yet available.[14] Biomarkers are related to progressivity and mortality due to COVID-19.[15] Huang et al., 2020 showed an increase in d-dimer concentrations was associated with an increased risk of hypercoagulability and was a predictor of mortality in hospitals.[16] Ponti 2020 showed C-reactive proteins (CRPs) as inflammatory markers are associated with the severity of COVID-19.[14] Biomarkers can be an efficient tool for prognostic stratification of COVID-19 patients, but limited information about which biomarkers can provide better prognostic value.[15] This study aimed to analyze the relation of D-dimer, Hs (high sensitivity) CRP and the use of angiotensin-converting enzyme (ACE) inhibitor drugs to severity, reinfection, and mortality of COVID-19 patients.

METHODS

This research is an analytical observational study with a retrospective cohort approach. This study analyzed the relation between D-dimer, Hs-CRP, and using ACE inhibitor drugs to severity, reinfection, and mortality of COVID-19 patients. The study was conducted during November 2022 to January 2023. Consecutive sampling technique was used for this study. The samples in this study were moderate, severe, and critical confirmed COVID-19 patients undergoing treatment at Dr. Moewardi Surakarta Hospital from January to March 2022 using secondary data from medical records with total 524 patient's medical records.

The inclusion criteria are patients over ≥18 years old who were diagnosed with moderate, severe, or critical COVID-19 from RT-PCR or rapid diagnostic antigen (RDT-Ag) examination. Living patients will be observed for reinfection until November 2022. The exclusion criteria are incomplete medical record data, patients or families cannot be contacted, and patients diagnosed with COVID-19 reinfection more than November 2022. D-dimer levels, Hs-CRP levels, and the use of ACE inhibitors when patients were treated at Dr. Moewardi Surakarta Hospital were collected. Variables were analyzed for the relationship to the severity, reinfection, and mortality of COVID-19 patients.

The author submitted research approval to the Ethics Eligibility Committee of Dr. Moewardi Surakarta Regional General Hospital before the research was conducted. The research data were analyzed with IBM Statistical Package for the Social Sciences (SPSS) Statistics Version 22 and the results were significant when the p value was <0.05. The research data were carried out analytical distribution tests with the Kolmogorov-Smirnov test because the number of samples was more than 50. The optimal cut-off value, sensitivity, and specificity of D-Dimer and Hs-CRP levels were assessed through the ROC curve. In this study, categorical data samples were analyzed with the chi square test, while numerical data used the mann whitney test. Multivariate analysis uses logistic regression test.

RESULTS

Subject characteristic

This study involved 517 confirmed COVID-19 patient medical records. Majority of COVID-19 patients aged 18-59 years (75.24%), male (53.19%), and were not health care workers (97.87%). Confirmed COVID-19 patients had cardiovascular disease (17.02%), Diabetes mellitus (17.02%). and other comorbidities such as malignancy, hypertension, kidney disorders, stroke, autoimmune (SLE), HIV, hepatitis, trauma and pregnant conditions

(50.29%). The use of ACE inhibitors in COVID-19 patients was 110 patients (21.28%). COVID-19 patients treated in the January to March 2022 were 361 patients (moderate severity) and 156 patients (31.17%). As 88.59% were had been vaccinated. The number of covid-19 patients who lived was 332 patients (64.22%) and those who experienced reinfection were 17 patients (5.1%). An overview of the characteristics of the subject of study can be seen in table 1.

Table 1. Subject characteristic

Variable	Total	%
Age		
≥ 60 years old	128	24.76
18-59 years old	389	75.24
Sex		
Male	275	53.19
Female	242	46.81
Occupation		
Non Health Care Worker	506	97.87
Health Care Worker	11	2.13
Cardiovascular Disease		
Yes	88	17.02
No	429	82.98
Diabetes melitus		
Yes	88	17.02
No	429	82.98
Other Comorbid		
No	257	49.71
Yes	260	50.29
Malignancy	56	10.83
Hypertension	45	8.70
Kidney disease	43	8.38
Stroke	23	4.45
Autoimune	10	1.93
HIV	9	1.74
Hepatitis	6	1.16
Others (<5 pasien/kasus)	64	12.38
Using ACE *inhibitor*		
Yes	110	21.28
No	407	78.72
Severity		
Not severe	361	69.83
Severe	156	31.17
Vaccination status		
Not yet	59	11.41
Already	458	88.59
Mortality		
Yes	185	35.78
No	332	64.22
Reinfection		
Yes	17	5,1
No	315	94,8

The cut off of Hs-CRP and D-Dimer values is determined using the receiver operating characteristic (ROC) curve. The Hs-CRP level has an Area under curve (AUC) value of 0.598. Hs-CRP has a sensitivity of 56.4% and a specificity of 54.0% to predict 59.8% of the severity of COVID-19. Hs-CRP cut-off values of ≥4.59 mg/dl with p=<0.001 (p<0.01) indicate Hs-CRP values ≥ 4.59 mg/dl are significant as predictors of severity of COVID-19 patients. Based on the severity compared to the results of the Hs-CRP and D-Dimer examinations, the ROC curve results were obtained.

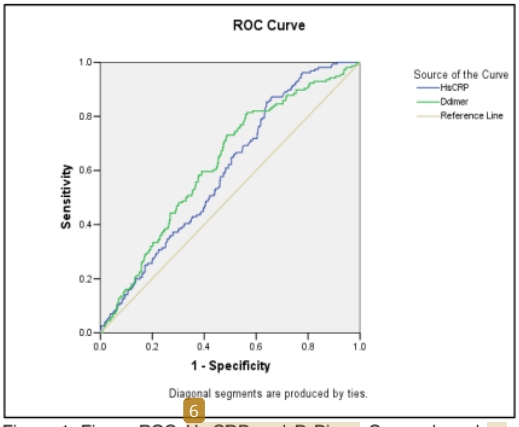

Figure 1. Figure ROC Hs-CRP and D-Dimer Curves based on Severity of COVID-19 patients.

D-Dimer levels based on the ROC curve have an AUC value of 0.626, which means that D-Dimer is able to predict 62.6% of the severity of COVID-19 with a sensitivity of 59.6% and a specificity of 60.1%. A cut-off value of ≥2435.00 with p=<0.001 (p<0.01) indicates that D-Dimer≥ 2435 ng/ml has significant results for the severity of COVID-19 patients.

Hs-CRP, D-Dimer, and Use of ACE inhibitor to the severity of COVID-19 patients

This study divided COVID-19 patients into two groups of analysis based on the degree of severity. Severe patients (COVID-19 severe and critical severity) about 156 patients and not severe patients (COVID-19 moderate severity) about 361 patients. Patients with severe degrees had average Hs-CRP levels of 9.19 ± 0.01 and average D-Dimer levels of 4506 ± 4774.91. The relation of Hs-CRP, D-

Dimer levels, and the use of ACE inhibitors to the severity of COVID-19 patients using chi square in bivariate analysis and logistic regression in multivariate analysis. Bivariate analysis showed Hs-CRP levels ≥4.59 mg/dl (OR=1.52; 95%CI=1.04-2.22; p=0.029) had a significant association with the severity of COVID-19 patients with a 1.52 times higher risk of developing severe COVID-19 rather than patients with HS-CRP levels <4,59 mg/dl. However, multivariate analysis showed Hs-CRP levels ≥4.59 mg/dl (OR=1.21; 95%CI=0.81-1.81; p=0.341) were not significant with the severity of COVID-19 patients with p>0.05.

Analysis of D-Dimer levels ≥2435 ng/ml showed a significant result on bivariate analysis (OR=2.22; 95%CI=1.52-3.26; p=<0.001) and multivariate analysis (OR=2.05; 95%CI=1.38-3.06; p=<0.001) to the severity of COVID-19 patients. Patients confirmed COVID-19 with D-Dimer levels ≥2435 ng/ml have a 2-fold risk having severe COVID-19. The use of ACE inhibitors showed no significant association in the results of bivariate or multivariate analysis. The results analysis of relation between Hs-CRP, D-Dimer, and the use of ACE inhibitors to severity of COVID 19 patients can be seen in table 2.

Table 2. Relation Hs-CRP, D-Dimer, and ACE inhibitor use to mortality of COVID-19 patients

Variable	Severity		Bivariat		Multivariat	
	Severe (n=156)	Not Severe (n=361)	OR (95%CI)	Prob.	OR (95%CI)	Prob.
Hs-CRP						
≥4.59	88	166	1.52 (1.04-2.22)	0.029*	1.21 (0.81-1.81)	0.341
<4.59	68	195	1	-	1	-
D-Dimer						
≥2435	93	144	2.22 (1.52-3.26)	<0.001**	2.05 (1.38-3.06)	<0.001**
<2435	63	217	1	-	1	-
Using ACE *inhibitor*						
Yes	35	75	1.10 (0.70-1.74)	0.672	-	n/s
No	121	286	1	-		

Hs-CRP, D-Dimer, and ACE Inhibitor Use to COVID 19 mortality

Hs-CRP levels ≥4.59 mg/dl showed a significant association on bivariate analysis ((OR=2.13; 95%CI=1.47-3.07; p=<0.001) and multivariate analysis (OR=1.82; 95%CI=1.23-2.69; p=0.003) to mortality of COVID-19 patients with p value<0.01. Confirmed COVID-19 patients with Hs-CRP levels ≥4.59 mg/dl had a 1.82 times higher risk of mortality rather than Hs-CRP levels<4.59 mg/dl.

Analysis of D-Dimer levels ≥2435 ng/ml either bivariate (OR=3.04; 95%CI=2.09-4.42; p=<0.001) or multivariate (OR=2.89; 95%CI=1.95-4.27; p=<0.001) showed a significant association to mortality of COVID-19 patients with p value <0.05.

Confirmed COVID-19 patients with D-Dimer levels ≥2435 ng/ml had a 2.89-3.04 times higher risk of mortality. The analysis showed Hs-CRP and D-Dimer can be considered as biomarkers predictors of mortality in COVID-19 patients.

The use of ACE inhibitors in bivariate analysis showed insignificant results (OR=0.55; 95%CI=0.46- 1.13; p=0.154) due to p value >0.05. The results of multivariate analysis show significant results (OR=0.55; 95%CI=0.33-0.89; p=0.015) so that the use of ACE inhibitors is a protective factor from mortality. Confirmed COVID-19 patients who used ACE inhibitors have 0,55 lower risk for mortality. The analysis results of the relation between Hs-CRP, D-Dimer, and the use of ACE inhibitors to mortality of COVID-19 patients can be seen in table 3.

Table 3. Relation of Hs-CRP, D-Dimer, and using ACE inhibitor to mortality of COVID-19

Variable	Mortality		Bivariat		Multivariat	
	Yes (n=185)	No (n=332)	OR (95%CI)	Prob.	OR (95%CI)	Prob.
Hs-CRP						
≥4.59	113	141	2.13 (1.47- 3.07)	<0.001**	1.82 (1.23-2.69)	0.003**
<4.59	72	191	1	-	1	-
D-Dimer						
≥2435	117	120	3.04 (2.09- 4.42)	<0.001**	2.89 (1.95-4.27)	<0.001**
<2435	68	212	1	-	1	-
Using ACE *inhibitor*						
Yes	33	77	0.72 (0.46- 1.13)	0.154	0.55 (0.33-0.89)	0.015*
No	152	255	1	-	1	-

Hs-CRP, D-Dimer, and ACE Inhibitor Use to COVID 19 Reinfection

The study found that of the 332 confirmed COVID-19 patients who were alive, 17 patients (5%) had reinfection. Bivariate analysis of Hs-CRP levels ≥4.59 mg/dl (OR=1.22; 95%CI=0.46- 3.24; p=0.694) showed no association with the incidence of reinfection of COVID-19 patients with p value>0,05. D-Dimer analysis ≥2435 ng/ml to COVID-19 reinfection on bivariate analysis (OR=0.72; 95%CI=0.25- 2.11; p=0.553) showed no association with the incidence of reinfection of COVID-19.

Use of ACE inhibitors (OR=3.11;95%CI=1.16-8.36); p=0.034) in bivariate analysis obtained significant results in COVID-19 reinfection. Patients taking ACE inhibitors had a 3,1 times higher risk of developing reinfection than patients who didn't use ACE inhibitors. However, multivariate anaysis of Hs-CRP, D-Dimer, and ACE inhibitor showed no significant result to COVID-19 reinfection with p value > 0,05. The results of the analysis are shown in table 4.

Table 4. Hs-CRP relationship, D-Dimer, and ACE inhibitor use to Reinfection of COVID-19 patients

Variable	Reinfection		Bivariat		Multivariat	
	Yes (17)	No (315)	OR (95%CI)	Prob.	OR (95%CI)	Prob.
Hs-CRP						
≥4.59	8	133	1.22 (0.46- 3.24)	0.694	-	n/s
<4.59	9	182	1	-		
D-Dimer						
≥2435	5	115	0 .72 (0 .25- 2.11)	0.553	-	n/s
<2435	12	200	1	-		
Using ACE *inhibitor*						
Yes	8	70	3.11 (1.16-8.36)	0.034*	2.42 (0.63-9.31)	0.197
No	9	245	1	-	1	-

DISCUSSION

Analysis subject characteristics

Majority COVID-19 confirmed patients in this study were men (53.19%) and has accordance with the research of Djaharuddin et al., 2020 in Indonesia.[13] Zhou's 20202 study showed higher ACE2 expression in men of Asian race.[17] Bwire 2020 explained men had higher ACE2 expression, immunological differences supported by women's production of hormones and the X chromosome as a protective effect, as well as men's lifestyles such as smoking.[18] High ACE2 receptors facilitate the entry of the SARS-CoV-2 virus that causes men to be more vulnerable against COVID-19 infection compared to women.[19] Sex hormones including estrogen and

testosterone have a direct effect on the immune system that makes men more susceptible to COVID-19 infection.[20] The majority of COVID-19 patients aged less than 60 years (75.24%) and non-health workers (97.87%) because this is a productive age with higher social activity.[18] Kuwari et al., 2021 found non-health care workers were more susceptible to COVID-19 due to lack of awareness of precautions such as avoiding crowds, wearing masks, or washing hands.[21]

Confirmed COVID-19 patients in these patients mostly have comorbidities especially cardiovascular disease, DM, and other comorbidities. Fathi et al., 2021 states comorbidities are considered as a risk factor for infection of COVID-19 patients.[22] Comorbid involvement causes patients to be at higher risk of dying from COVID-19 infection.[13,22,23] Djaharuddin's 2020 found hypertension, cardiovascular disease, and diabetes to be comorbidities that are often found in COVID-19 patients.[13] ACE2 receptors were found in cardiomyocytes.[24,25] ACE2 levels in circulation increased in patients with hypertension, cardiovascular disease, and diabetes causing patients with such comorbidities to be more susceptible to infection COVID-19. [24,26] Comorbid diabetes is a risk factor for the severity of the disease and poor outcomes in COVID-19 patients.[27] COVID-19 patients with non-severe degrees totaled 361 patients (69.83%) and 88.59% of patients had been vaccinated. Islam 2022 showed that vaccinated patients had a much greater chance of developing moderate infections than unvaccinated patients.[9] Vaccination will increase immunity, as patients who have received at least 1 dose of the vaccine have higher plasma anti-receptor binding domain (RBD) antibodies and a nearly 50-fold increase in neutralizing activity.[28] Confirmed COVID-19 patients who are alive and experiencing reinfection 17 patients (5.1%). Cavanaugh 2021 suggests vaccination can lower the risk of reinfection.[29]

Severity Analysis of COVID-19 patient

This study showed cut off value of Hs-CRP ≥ 4.59 mg/dl was significant to severity of COVID-19. This study had a lower cut off value because serum CRP is an acute phase protein synthesized by the liver due to IL-6 stimulation. Hs-CRP levels were influenced by gender, ethnicity, and acute degree of the disease, and time of taking.[30] The samples in this study were mostly not severe COVID-19 patients and the time of blood sampling for serum examination was not observed as an influenced factors. Bivariate analysis between severity and Hs-CRP levels ≥4.59 mg/dl showed a significant association. The more severe the severity of COVID-19, the more Hs-CRP values will increase.[15,31] Multivariate analysis showed that Hs-CRP levels ≥4.59 mg/dl were not significant to severity of COVID-19. This can be happened because Hs-CRP is a biomarker influenced by age, gender, smoking, weight, fat levels, blood pressure, and liver damage.[16] Patients with myocardial infarction, stress, trauma, infection, inflammation, surgery, or malignancy can cause elevated Hs-CRP levels to be less specific.[30] D-Dimer levels based on the ROC curve have cut-off value of ≥2435 ng/ml. The research of He et al., 2021 has a cut-off not much different, namely 2,025 mg / mL.25

D-Dimer levels ≥2435 ng/ml has significant relation to severe COVID-19 in both bivariate and multivariate analyses.[32,33] The increase in D-dimer levels in COVID-19 patients was mainly due to the release of pro-inflammatory cytokines that caused inflammatory storms. Levels of pro-inflammatory cytokines such as IL-2, IL-7, G-CSF, IP-10, MCP-1, MIP-1A and TNF-α in plasma are higher especially in severe COVID-19 patients. T cells, macrophages, and natural killer cells cause this release supported by studies of more than 150 inflammatory cytokines and chemical mediators resulting in microvascular system damage, and abnormal activation of the coagulation system, pathological manifestations of systemic vasculitis and extensive microthrombosis.[24,34] Hypoxia that occurs in severe COVID-19 patients triggers molecular and cellular pathways that cause thrombosis.[35] Sepsis that occurs in COVID-19 patients severe affects blood clotting, such as elevated levels of PAI-1, and fibrinolysis thus activating the coagulation cascade, as well as causing thrombosis.[32] The use of ACE

inhibitors showed no significant association with severity in neither bivariate nor multivariate analyses

Mortality analysis of COVID-19 patients

Bivariate and multivariate analysis showed Hs-CRP values ≥4.59 mg/dl had a significant association with mortality of COVID-19 patients. This research is supported by many studies that show Hs-CRP is a good predictive biomarker and correlates with a high risk of death in COVID-19 patients.[36,37] The study of Shabrawy et al., in 2021 proposed cutting off of Hs-CRP serum of more than 33.9 ng/L with a sensitivity of 76.5% and a specificity of 88.9% to predict mortality in COVID-19.[37] Ahirwar et al., in 2022 showed Hs-CRP more than 65.5 mg/L had a sensitivity of 93.8% and a specificity of 85.3% for predicting death in COVID-19.[38]

The cut-off value of D-Dimer in this study was ≥2435 mg/dl and the results of the analysis showed significant values for mortality of COVID-19 patients. Zhang's 2020 stated that D-Dimer values of more than 2 µg/mL were predictors of mortality of COVID-19 patients.[39] He 2021 stated that D-dimer values 2,025 mg/L as the optimal cut-off value of predictors of mortality of COVID-19 patients.[32] This study showed that D-Dimer ≥2435 ng/ml in COVID-19 patients had 2.89-3.04 times higher risk of mortality. Severe COVID-19 patients release more than 150 inflammatory cytokines and chemical mediators causing microvascular damage, abnormal activation of the coagulation system, pathological manifestations of systemic vasculitis and extensive microthrombosis.[24,34] Sepsis and severe hypoxia in COVID-19 patients increase in PAI-1 levels and fibrinolis causes thrombosis that increase D-Dimer level.[32,34,35] Gungor et al., 2021 showed D-Dimer levels at the beginning of hospitalization were associated with severity and could predict mortality.[33]

The use of ACE inhibitors is a protective factor of mortality. Angiotensin II production decreases due to ACE inhibitors increasing the production of Ang-(1–7) by ACE2 and activation of Mas receptors which act as anti-inflammatory and anti-fibrosis. The protective role by ACE inhibitors reduces lung injury thereby reducing severity and mortality.[40–42] Vasodilation, anti-inflammatory, antiproliferative, and antifibrotic effects by ACE2 receptors offset the effects of systemic damage from COVID-19.[43,44] The fourth edition of COVID-19 management guidelines and European society of cardiology suggest to continue the use of ACE inhibitors or ARBs in patients who are using, as it may decrease mortality rates and the need for mechanical ventilation in COVID-19 patients.[19,45]

Reinfection Analysis of COVID-19 patient

The study showed patients taking ACE inhibitors had a 3.1 times higher risk of developing reinfection. ACE2 levels in circulation increased in patients taking ACE inhibitor drugs.[26] The attachment and fusion of the virus into the host cell begins when the virus's S protein binds to the host cell's receptor binding domain (RBD) ACE2.[1,46] The affinity of the SARS-CoV-2 bond to ACE2 is 10-20 times stronger than that of SARS-CoV.[46] So that ACE inhibitor users facilitate the entry of SARS-CoV-2 which facilitates infection or reinfection of COVID-19.[26,41]Hs-CRP and D-Dimer biomarkers cannot be used as predictors of reinfection of COVID-19 patients.[4] Hs-CRP levels of ≥4.59 mg/dl and D-Dimer≥2435 ng/ml were not significant to the incidence of COVID-19 reinfection.

LIMITATION

This study obtained reinfection information by telephone, not based on whole genome sequencing examination due to limited facilities and infrastructure. In addition, because the data used medical records, researchers did not examine the length of use of ACE inhibitors against mortality effects that could be research biases.

CONCLUSION

COVID-19 patient with D-Dimer levels ≥2435 ng/ml had a 2-fold higher chance of experiencing severe COVID-19 and 3.04 times higher mortality compared to patients with D-Dimer levels < 2345 ng/ml. Patients with Hs-CRP levels ≥4.59 mg/dl had 1.52 times higher chance of experiencing severe

COVID-19 and 1.82 times higher mortality than Hs-CRP levels < 4.59 mg/dl. COVID-19 patients who taking ACE inhibitors had 3.1 times higher chance of developing COVID-19 reinfection, but had a 0.55 times lower risk of mortality.

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